issues were discussed. First, the Examiner introduced Applicants to U.S. Patent No. 5,866,363, issued to Pieczenik on February 2, 1999. This patent issued from Appl. No. 07/662,764, filed February 28, 1991, which purports to be a continuation-in-part (CIP) of Appl. No. 07/201,358, which purports to be continuation of 06/770,390, filed August 28, 1995. The Examiner indicated that the possibility of an interference between Pieczenik and Kauffman had been previously considered. However, in the Examiner's opinion Pieczenik and Kauffman could be distinguished from each other on the basis that Pieczenik's random oligonucleotide populations were truly "random," whereas Kauffman's, being described as "stochastic," were not (see the Examiner's hand-written notes from the Examiner interview, attached as Exhibit A).[1] Thus, both Kauffman and Pieczenik were issued as patents.

Applicants have since sought to provoke an Interference with Kauffman on the basis that Applicant's "random" oligonucleotide populations and methods of use thereof constitute subject matter which is the same invention as that described in Kauffman. The Examiner has raised two possible scenarios as a result of the Request for Interference in light of his earlier analysis pertaining to Pieczenik:

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[1] Applicants note that the file history of Pieczenik appears to contradict the interpretation of the Examiner. For instance, with regard to the UK patent application GB 2 183 661 A of Ballivet et al. (Kauffman is second-named inventor), Pieczenik argued in the Reply dated May 15, 1992 (attached as Exhibit B, pp. 20-21), that Ballivet refers to "stochastic genes or fragments of stochastic genes [capable of producing] completely new proteins." Pieczenik distinguished his invention from Ballivet by arguing that, in contrast, the proteins formed therein are not "completely new" but "mostly old."

(1) If Kauffman's "stochastic" oligonucleotide populations are the same patentable subject matter as the "random" oligonucleotides of the present application, then should Pieczenik, who also discloses "random" oligonucleotides, also be in the interference?

(2) On the other hand, if "stochastic" as used in Kauffman is different from "random" as used in the present invention, would this mean that (i) an interference between Kauffman and the present application is not warranted, and, moreover, (ii) that Pieczenik would be prior art under 35 U.S.C. §102(e) against the present application (because both teach the use of "random" oligonucleotide populations)?

To summarize at the outset, it is Applicant's position that "stochastic" as it is used in Kauffman encompasses random sequences, and that an interference between the Kauffman patents and applications and the present application is warranted. Furthermore, Applicants believe that the Examiner was correct in not declaring an interference between Kauffman and Pieczenik, albeit for reasons different than the literal meanings of "stochastic" and "random." Rather, Pieczenik should not be included in the Interference because the Pieczenik claims are not entitled to benefit of priority of the grandparent application, and are directed to an apparently later-invented separately patentable species within the genus claimed by Kauffman and the present Applicants. The fact that the Pieczenik claims are only entitled to the benefit of the CIP filing date (February 28, 1991) also removes Pieczenik as a 102(e) reference. The issues are addressed in the order presented above for the Examiner's convenience.

1. **"Stochastic" as it is used in Kauffman encompasses random sequences**

Kauffman makes several statements during prosecution which make it clear that "stochastic" means or includes random. For instance, in the Response dated February 5, 1998, in the Kauffman '483 patent file history (Exhibit C), it is stated:

> **Included in the definition of the term stochastic is random.** As is known to those of skill in the art, this term means that the claimed populations are random and as such are diverse. Diversity is an inherent outcome of the random polymerization of, for example, nucleotide or oligonucleotide building blocks as compared to the polymerization of a defined specific sequence.
>
> In light of the teachings within the application, the phrase "at least partially stochastic polynucleotide sequences" is intended to include sequences which are random, as described above. In addition, the phrase can include a sequence, part of which is stochastically generated, and part of which is not stochastically generated. The part that is not stochastically generated can be a known or unknown sequence. The phrase can additionally include a sequence that contains a biased amount of any one or all of the four nucleotide triphosphate or other building blocks which comprise the polynucleotide sequence. [See pages 17-18. Emphasis added.]

Likewise, in the Response filed August 23, 1995, for the '323 patent (Exhibit D), it is stated:

> **For example, included within the definition of the term 'stochastic' is random.** As is known to those skilled in the art, this term means that claimed populations are diverse. Diversity is an inherent outcome of the **random polymerization** of, for example, nucleotide or oligonucleotide building blocks as compared to the polymerization of a defined or specific sequence. [See pages 18-19. Emphasis added.]

Similarly, in the Response filed June 10, 1996, for the '514 patent (Exhibit E, p. 13), Kauffman states in responding to a prior art rejection:

> [S]uch methods do not result in or suggest the production of **random, stochastic sequences as claimed in this invention.** General knowledge at the time of the invention did not teach or suggest the production of such **random, stochastic sequences.** [Emphasis added.]

Thus, it appears clear to Applicants that Kauffman's term "stochastic" includes random sequences given the comments that Kauffman himself makes during prosecution. Applicants respectfully remind the Examiner that the Federal Circuit has encouraged the PTO to give claims their "broadest reasonable interpretation" during prosecution. *In re Morris*, 127 F.3d 1048 (Fed. Cir. 1997) (*citing In re Prater,* 56 C.C.P.A. 1381, 415 F.2d 1393, 1404-05, 162 U.S.P.Q. (BNA) 541, 550-51 (CCPA 1969). It follows that "[l]imiting claims . . . to what is described in the specification . . . would conflict with this practice," and that the prosecution file history should also be considered in construing the claims. *In re Morris*, 127 F.3d at 1055.

Furthermore, it is also apparent from other comments made in the file history of the Kauffman patents that Kauffman defines "random" in a similar manner to Applicants. In the present invention, a "random" nucleotide sequence is formed "without regard to a wild type sequence" (see, for instance, claim 3, and the specification at page 8, lines 11-19 and at page 28, lines 1-4). Likewise, in the file history for Kauffman patent '514, in the Response dated

June 10, 1996 (Exhibit E, p. 16), it is stated:

> None of the cited art or general knowledge contains any specific suggestion to create stochastic sequences independent of "target sequences."

Similarly, in the Response dated May 24, 1996, for the '483 patent (Exhibit F, at pages 7-8), it is stated:

> **Sirotkin is directed to the mutagenesis of a known target DNA.** The mutagenesis methods described by Sirotkin result in a single randomly-located region in the target DNA with random substitute mutations. This mutagenesis is accomplished by adding two noncomplementary nucleotides to a primer and then incorporating these nucleotides into the template strand.
>
> **Applicants claim a process comprising the production of a population of stochastic or partially stochastic polynucleotide sequences.** Such populations are diverse in sequence and complexity and are produced by, for example, the random copolymerization or chemical coupling of nucleotide monomers. **Applicants claimed method does not utilize a template molecule nor does it result in substitution mutations within a single randomly located region within the target DNA.** [Emphasis added.]

Thus, not only does Kauffman describe the use of stochastically generated nucleotide sequences which are random in nature, it is clear that Kauffman uses the term "random" in the same manner as Applicants; that is, to refer to a sequence generated without regard to a wild type sequence. Accordingly, it is Applicants' belief that Kauffman and the present application disclose and claim the same invention, and that an Interference should be declared between the

Kauffman patents and applications and the present application.

2. Pieczenik should not be included in the Interference, because Pieczenik is not entitled to benefit of priority of the grandparent application and is directed to an apparently later-invented separately patentable species within the genus claimed by Kauffman and the present Applicants.

Applicants agree with the Examiner that an Interference should not be declared between Kauffman and Pieczenik. However, Applicants would base this decision on reasons other than the literal meanings of "stochastic" and "random." Pieczenik should not be included in the Interference because the Pieczenik claims are not entitled to benefit of priority to the grandparent application. Therefore, Pieczenik is directed to an apparently later-invented separately patentable species within the genus claimed by Kauffman and the present Applicants.

There is ample evidence that Pieczenik did not teach how to make and use a random population of oligonucleotides until the CIP application was filed on February 28, 1991. First, to emphasize the vast amount of material added to the disclosure when the 07/662,764 CIP application was filed, Applicants have attached as Exhibit G a CompareRite®-generated

document of the CIP application where the newly added material is underlined and bolded.[2] Note that Examples IV and V are clearly new material when compared to the original specification. Yet, Examples IV and V were required for one of skill in the art to make and use the invention, and Pieczenik stated as much during prosecution.

To teach one of skill in the art how to use the oligos of his invention, Pieczenik had to teach how to express those oligos to make peptides, and how to display such peptides such that they could be screened for antibody epitopes. This is the only utility described in the application. Examples IV and V concern the use of filamentous phage vectors for displaying peptide sequences on the surface of host cells. It was not until these examples were added that Pieczenik presented a feasible means of performing the screening methods of the invention.

Indeed, during the prosecution of the Pieczenik patent, the previous Examiner rejected the claims under 35 U.S.C. 112, first paragraph, as failing to describe the expression of random oligonucleotides to produce peptides (Office Action dated June 29, 1992). In response to this rejection, Pieczenik pointed to Example IV as demonstrating the insertion of oligonucleotides into the minor coat protein gene III of bacteriophage f1, and Example V as teaching the expression of an exemplary oligonucleotide within the pIII minor coat protein and detection with antibody (see Exhibit H, excerpts from Pieczenik Amendments filed October

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[2] CompareRite® is a computer program which compares two documents and highlights the differences. The material deleted from the first document as compared to the second is shown in brackets. The material added to the second document here is underlined and bolded.

29, 1992, and May 15, 1992). Pieczenik identifies no other example or disclosure which would teach the expression of peptides in such a manner that they may be screened with antibodies in order to identify a particular peptide of interest.[3] Only material added to the CIP disclosure is used to rebut the rejection.

In fact, George Pieczenik himself admits that he did not have evidence of the "operability of the invention" until he performed experiments with the filamentous phage system, as described in the Declaration of Pieczenik submitted with the Reply dated May 15, 1992 (Declaration was pursuant to 37 CFR 1.131; see p. 7, second full paragraph, attached as Exhibit I). There is significant evidence that he had not performed these experiments until after the grandparent application was filed. For instance, the Pieczenik Declaration was submitted along with others in order to antedate a prior art reference dated August, 1990, whereas no antedating Declarations were submitted in rebuttal to the Ballivet (Kauffman) reference, dated 1987. Furthermore, as described in his Declaration, Pieczenik used the data gathered from these experiments to seek the support of "potential corporate research sponsors"

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[3] Note that Pieczenik Example I describes a λgt11 system whereby oligonucleotides are inserted into the beta-galactosidase gene of λgt11. This is a lytic phage system (beta-galactosidase is not a secreted protein). Thus, in this system, peptides would be screened after cell lysis following phage infection. Peptides of interest would then need to be identified from among all proteins released from the host cell during lysis. Therefore, peptides of interest could not be screened free of all proteins released from the host cell during lysis. In his arguments to rebut the enablement rejection, Pieczenik does not assert that this system has been or could be used to screen random peptide libraries, but instead relies on the phage display system disclosed in the newly added material in his CIP.

admittedly some time "after the filing of USSN 770,390, filed August 25, 1985" (see Exhibit I, page 2). Moreover, he sent a draft manuscript describing these experiments to his attorney, Lorance Greenlee, along with a letter describing the manuscript as "fairly hot off the presses" (see Exhibit J, containing a Declaration by Lorance Greenlee also attached to the May 15th Response, and the letter from Pieczenik attached thereto). Because Lorance Greenlee only began representing Pieczenik in June of 1987, the draft manuscript could not have been "hot off the presses" any earlier than this date (see Exhibit J, paragraph 2).

Thus, the evidence suggests that Pieczenik did not believe, nor did he have evidence, that his invention would work at the time the grandparent application was filed. Moreover, the disclosure which describes the enabling information was not added until the CIP application was filed on February 28, 1991.[4] It is well established that such information must be adequately described in the application in order to satisfy the requirements of 35 U.S.C. §112, first paragraph. "To qualify for an earlier filing date, section 120 requires, *inter alia*, that the earlier-filed U.S. patent application contain a disclosure which complies with 35 U.S.C. § 112, ¶ 1 for each claim in the newly filed application . . . Under 35 U.S.C. § 112, ¶ 1, and consequently under 35 U.S.C. § 120 as well, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention . . . In sum, 35 U.S.C. § 120 requires an applicant to meet the disclosure

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[4] Indeed, Pieczenik did not refer to his oligonucleotides as "random" until the CIP was filed (see Exhibit G, material added to pages 6-7).

requirement of § 112, ¶ 1 in a single parent application in order to obtain an earlier filing date for individual claims." *Studiengesellschaft Kohle m.b.H v. Shell Oil Co.*, 42 USPQ2d 1674, 1677 (Fed. Cir. 1997).

Applicants respectfully submit that Pieczenik is not entitled to benefit of priority to the grand-parent application, 06/770,390, because that application fails to satisfy the requirements of 35 U.S.C. §112, first paragraph. Thus, Pieczenik is only entitled to a priority date which is almost 5 years after the present application and Kauffman.

In view of the above, Pieczenik is not properly cited as prior art against Applicants' claims. Moreover, the attached Declaration provides a further reason why Pieczenik is not properly used to reject Applicants' claims.

It is also clear that Pieczenik should not be included in the requested Interference because it is directed to a separately patentable species within the genus described in the present application and Kauffman.

For instance, while the present invention is directed to screening random nucleic acids and peptides in general for a variety of desired biological functions, Pieczenik in particular concerns the screening of short random peptide populations (4 to 12 amino acids) specifically for antigenic epitopes using a particular expression system, a filamentous phage vector. As explained above, the filamentous phage vector system, required for the direct identification of discrete epitopes using antibody screening as proposed by Pieczenik, was not enabled until the Pieczenik CIP application was filed on February 28, 1991. The Patent & Trademark Office

has made it clear that a genus does not always anticipate a claim to a species within the genus. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). "The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." MPEP §2144.08 (citing *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).

Thus, Pieczenik appears to be a separately patentable species within the genus disclosed in Applicant's application. That issue, however, is irrelevant to the present situation, which warrants immediate resolution of the following question: whether the generic disclosure of screening random oligonucleotides or peptides for any desired biological activity belongs to Applicants or to Kauffman.

In summary, this Reply is believed to address all the issues raised in the Examiner Interview. As a result it can now be concluded that (1) an Interference between Kauffman and the present application should go forward because Kauffman and the present application describe the same patentable invention; and (2) Pieczenik should not be added to the Interference because Pieczenik is directed to a separately patentable species within the genus claimed in the present application and Kauffman.

Should the Examiner wish to discuss these issues further, he is respectfully requested to contact the undersigned so that a second interview may be arranged. Applicants understand that the Examiner's schedule is particularly busy at the moment and that an Interference involving the five patents of Kauffman and any applications unbeknownst to Applicants is a

significant project. Therefore, Applicants would be more than happy to assist the Examiner in any way possible such that the Interference between Kauffman and the present application may be expedited.

Respectfully submitted,

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Date: September 24, 1999